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| EXAMINER | |
|---|---|
| EWOLDT, GERALD R | |

| ART UNIT | PAPER NUMBER |
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| 1644 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/535,395 | SEVE ET AL. | |
| | Examiner | Art Unit | |
| | G. R. Ewoldt, Ph.D. | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *39,40 and 46-55* is/are pending in the application.

4a) Of the above claim(s) *52-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39,40,46-51 and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 6/26/09 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment, remarks, and substitute drawings filed 6/26/09 have been entered.

2. Newly added Claims 52-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions.

Claims 39, 40, 46-48, and newly added Claims 49-51 and 55 are under examination.

3. In view of Applicant's amendment, the previous rejections under the second paragraph of 35 U.S.C. 112, as well as the first paragraph of 35 U.S.C. 112, for the introduction of new matter into the claims, have been withdrawn.

4. Applicant's Replacement Drawing are acknowledged. Figures 1, 3, and 4 are acceptable. Figure 2 is incomplete showing just a small portion of the original figure. Accordingly, Figure 2 remains objected to.

5. The specification is objected to for the following informalities:

A) The disclosure is objected to because it contains embedded hyperlinks and/or other forms of browser-executable code. See, for example, pages 9 and 34 of the specification. Applicant is required to delete the embedded hyperlinks and/or other forms of browser-executable code. See MPEP § 608.01.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 39, 40, 46-48, and newly added Claims 49-51 and 55 stand/are rejected under 35 U.S.C. § 112, first paragraph. Specifically, one skilled in the art would not know how to use the claimed invention.

As set forth previously, the specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

*In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. With these teachings in mind, an enabling disclosure, commensurate in scope with the breadth of the claimed invention, is required.

A review of the instant specification reveals nothing about the detection of autoantibodies specific for the proteins of SEQ ID NOS:2 and 7-10, nor even if such autoantibodies exist. While it is asserted that the ZnT-8 protein of SEQ ID NO:2 might comprise a marker for the β cells of pancreatic islets of Langerhans, even this minimal assertion is not confirmed in the instant specification. First note that in Example 2 only whole pancreas was probed for the expression of ZnT-8 mRNA. Thus, the example is silent regarding β cell-specific expression. In Example 3 only β cells were probed for ZnT-8 mRNA expression, thus, the example is silent regarding whether or not other cells of the pancreas also express the protein. The data of Examples 4-7 are unrelated to the method of the instant claims. Finally note even the data that are provided cannot be interpreted as the figures are essentially illegible.

Accordingly, the skilled artisan would not know how to use the claimed method.

A set forth in *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297, 1302 (CAFC 2005), enablement cannot be established unless one skilled in the art "would accept without question" an Applicant's statements regarding an invention, particularly in the absence of evidence regarding the effect of a claimed invention. Specifically:

"As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under

> section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

Applicant's arguments, filed 6/26/09, have been fully considered but are not found persuasive. Applicant argues that the newly amended claims are enabled, particularly in light of the teachings of Wenzlau et al. (2007) and Wenzlau et al. (2008).

> Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, **when filed**, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention (emphasis added) (**MPEP 2164.01 [R5]).**
>
> A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, **at the time the application was filed**, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation (emphasis added) (**MPEP 2164.01(a)).**
>
> Once the examiner has weighed all the evidence and established a reasonable basis to question the enablement provided for the claimed invention, the burden falls on applicant to present persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention **using the application as a guide** (emphasis added) (**MPEP 2164.05).**
>
> Applicant may submit factual affidavits under 37 CFR 1.132 or cite references to **show what one skilled in the art knew at the time of filing the application.** (emphasis added) (**MPEP 2164.05).**

The MPEP makes clear that first, an invention must be enabled at the time of filing and second, the specification itself must teach how to make and use the claimed invention. In the instant case neither requirement has been met. The instant

application has a priority date of 11/18/02. Thus, 2007 and 2008 publications cannot provide enablement as of the time of filing.

Turning to the specification itself, it neither discloses nor enables the claimed method. The Inventors have cloned and expressed a gene named *ZnT-8* which they predict is involved in zinc accumulation in insulin containing vesicles. They have further computer modeled the expressed protein to have six transmembrane domains. While the protein appears to be expressed in pancreas (Figure 1) there is no indication of whether or not said expression is limited to islets. While expression is shown in human islets (Figure 2) no controls are shown that expression is limited to pancreatic islet cells. additionally, the word "autoantibodies" appears just twice in the application, once in original Claim 29 and once at page 20. In neither instance is the word "autoantibodies" disclosed in the context of detecting type 1 diabetes.

The specification clearly does not disclose the assay of the instant claims. Further, the specification establishes no links between the ZnT-8 protein and diabetes, nor does it provide any evidence that autoantibodies to the proteins encoded by *ZnT-8* exist in diabetic patients, or that should such autoantibodies exist that they could be employed in an assay for the detecting of type 1 diabetes. Accordingly, the rejection has been maintained.

8. The following are new grounds for rejection necessitated by Applicant's amendment.

9. Claims 39, 40, 46-48, and newly added Claims 49-51 and 55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter written description rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) A method of detecting type 1 diabetes comprising detecting the presence of complexes comprising autoantibodies specific for ZnT-8 or an antigenic fragment thereof, said method

comprising contacting serum from a subject with ZnT-8 or an antigenic fragment thereof (Claim 39).

B) A method of detecting ZnT-8 autoantibodies comprising detecting the presence of complexes comprising autoantibodies specific for ZnT-8 or an antigenic fragment thereof, said method comprising contacting serum from a subject with ZnT-8 or an antigenic fragment thereof, wherein the detection of a complex is indicative of an increased risk of type 1 diabetes (Claim 55).

Applicant cites pages 15, 19, and 20, and Claim 24, 25, and 29 in support.

A review of the cites does not reveal the claimed method.

Page 20 discloses only, "The invention also relates to the use of the protein or of the protein fragment as defined above, for measurements by means of immunochemical and immunoenzymatic methods, and also the search for autoantibodies directed against the protein according to the invention". This is not the claimed method.

Page 19 discloses only, "Preferably, a protein according to the invention is a protein comprising or having the sequence SEQ ID NO. 2 (corresponding to the protein encoded by the *ZnT-8* gene)." This is not the claimed method.

"A subject of the invention is also a fragment of the protein as defined above, characterized in that it is selected from the group consisting of the sequences SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9 and SEQ ID NO. 10."

Page 15 discloses only, "mutations include in particular deletions, insertions or non-conservative substitutions in codons corresponding to amino acid residues located in a domain that is essential for the biological activity of the protein."

"Thus, a subject of the invention is a method for determining the transcription profile of the gene…". This is clearly unrelated to the claimed method.

Claims 24, 25, and 28 recite:

24. The protein as claimed in Claim 23, characterized in that it comprises or has the sequence SEQ ID NO. 2.

25. A fragment of the protein as claimed in claim 24, characterized in that it is chosen from the sequences SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9 and SEQ ID NO. 10.

28. The use of a protein or of a protein fragment as claimed in any one of claims 23 to 25 or of a protein chip as claimed in claim 26, for detecting the presence of antibodies directed against said protein in the serum of an individual.

None of these claims even recite a method. Claim 28 might support an assay method, however, it does not support the limitations of the claims. For example, it does not support the detecting of "complex formation". Neither does it support a method employing generic "antigenic fragments" of ZnT-8. Finally, none of the cites relate ZnT-8, or autoantibodies thereto, to type 1 diabetes, either the detecting of, or correlating to an increased risk of.

Regarding Applicant's argument against a previous rejection that the correlation between autoantibodies to pancreatic antigens and type 1 diabetes was well known as of the filing date of the instant application, said argument would seem to provide additional support for the Examiner's position that a claimed invention must be enabled (i.e., satisfy the requirements under 35 U.S.C. first paragraph) as of the filing date of the application. Regarding the well known relationship of autoantibodies to pancreatic antigens and type 1 diabetes, Applicant appears to be arguing that the relationship would render the claimed method obvious. It is well known that obviousness is not the standard as regards an adequate written description.

10. Claims 39, 40, 46-48, and newly added Claims 49-51 and 55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Under *Vas-Cath, Inc. v. Mahurkar* , 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description

requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession* of the invention, and that the invention, in that context, is whatever is now claimed.

There is insufficient written description to show that Applicant was in possession of the "antigenic fragments" of ZnT-8 of the claims.

Regarding the claimed fragments, said fragments are described by function, but no common structure has been disclosed. The only requirement appears to be that the fragments be antigenic. It is well known that depending upon context, e.g., species of animal or whether or not the fragment is employed with an adjuvant, almost any protein fragment might be rendered "antigenic". Accordingly, the genus of fragments employed in the claimed method could be quite large. Absent a common structure and function a representative number of species of the claimed fragments must be disclosed. But it is unclear whether or not any antigenic fragments of ZnT-8 are actually disclosed given the curious way in which Examples 6 and 7 are worded. While four fragments appear to have been used to immunize rabbits in Example 6, the results of the immunizations are not disclosed. A careful reading of Example 7 shows it to be prophetic, i.e., the labeling of an antibody that Applicant does not yet possess. Accordingly, given that no examples of antigenic fragments of ZnT-8 are actually disclosed, one of skill in the art would conclude that the specification fails to disclose a representative number of species to describe the antigenic fragment genus of the claims. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on (571) 272-0841.

13. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval

(PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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